

Intensity-modulated radiation therapy (IMRT): a clinical reality for cancer treatment, “any fool can understand this”

The 2004 Silvanus Thompson Memorial Lecture

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A brief note on Silvanus Thompson

The name of Professor Silvanus Thompson will be very well known to older members of the professions that comprise the British Institute of Radiology and to those interested in radiological history and the history of physics. Others may, however, appreciate a brief synopsis [1] of the man who was the first President of the Röntgen Society (later incorporated into the British Institute of Radiology).

Silvanus Thompson was born in 1851 and, a lifelong Quaker, was appointed the science master at the Quaker School at Bootham in York in 1873. His major interests were light, optics and electromagnetism (Figure 1) and in 1876 he was appointed as a lecturer in physics at University College, Bristol where he became Professor in 1878. Also in 1878 the City and Guilds of London Institute for the Advancement of Technical Education was founded with Finsbury College as a teaching institution. Thompson was its Principal and Professor of Physics for 30 years and cared passionately about the technical education of scientists and engineers. He was a renowned teacher, skilled lecturer and wrote many biographies of well known scientists such as Edison, Faraday, Lord Kelvin and William Gilbert. His book collection of now rare nineteenth and early twentieth century titles is preserved at the Institute of Electrical Engineers. He repeated Röntgen's experiments the day after the discovery was announced in the UK and gave the first public demonstration in London on March 30th 1896.

Perhaps more surprisingly he is better known to the wider scientific community for his little book *Calculus made easy* (Figure 2) first published in 1910 and still available from web outlets such as Amazon.com. He wrote in its preface:

“Considering how many fools can calculate, it is surprising that it should be thought either a difficult or a tedious task for any other fool to learn how to master the same tricks.

“Some calculus-tricks are quite easy. Some are enormously difficult. The fools who write the text-books of advanced mathematics – and they are mostly clever fools – seldom take the trouble to show you how easy the easy calculations are. On the contrary, they seem to desire to impress you with their tremendous cleverness by going about it in the most difficult way.

“Being myself a remarkably stupid fellow, I have had to unteach myself the difficulties, and now beg to present to my fellow fools the parts that are not hard. Master these

thoroughly and the rest will follow. What one fool can do, another can.”

Perhaps we can take this as a nice introduction to intensity-modulated radiation therapy (IMRT) if we substitute the acronym “IMRT” for “calculus”. Certainly many of the papers on the physics of IMRT are extraordinarily complicated and one might even feel some make them deliberately so. However, some of the classic papers, whilst not trivial, present the main concepts that are all that many want or need to know.

The author's opinion is that there is really no need here for another detailed review of the physics and clinical application of IMRT. There are plenty written already including books by Webb [2–5], the book from the 2003 AAPM Summer School [6], the report from the IMRT Cooperative Working Group on IMRT in November 2001 [7] which can be read as a tutorial on the subject and the IMRT Subcommittee of the AAPM Radiation Therapy Committee report on guidance on IMRT implementation [8]. A joint document from ASTRO and AAPM has overviewed the whole process of implementing clinical IMRT [9]. The British Institute of Radiology has just



Figure 1. Silvanus Thompson and apparatus for “mesmerising” (stimulating retinal light by magnetism).

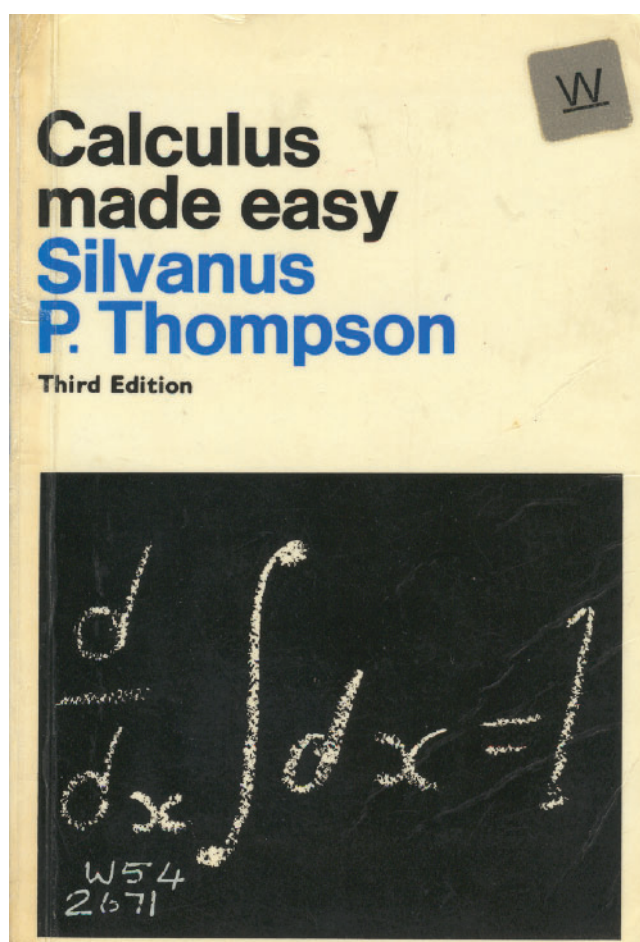


Figure 2. Silvanus Thompson's famous book on calculus.

published a 7-part set of review articles on IMRT in the *British Journal of Radiology* [10–16]. These detail literally thousands of primary references in the peer review literature.

In this paper, as in the 2004 Silvanus Thompson Memorial Lecture on May 19th 2004 I shall attempt to present, in simple terms, aspects of the physics and clinical implementation of IMRT.

Why IMRT?

The X-ray was discovered on November 8th 1895 and, within a year, treatment of cancer with ionising radiation had begun. It was quite well developed within 5 years with an important textbook published within 10 years [17]. For some 50 years or so “boxes” of high dose were created by crossfiring rectangular beams of radiation. Given most tumours are not rectangular, when the “box” was designed to encompass the tumour, unwanted irradiation of normal tissues in the corners of the box arose. Rotation therapy with rectangular open fields improved this to encompass the target within a cylinder of high dose. Devices such as blocking, to geometrically shape the fields, and the use of wedges and compensators, to modify the depth-dose characteristics, improved on this somewhat. However, the ability to “shrinkwrap” the high-dose volume to the target, as a piece of clingfilm would wrap an avocado pear, is the goal. It is only achievable, for volumes with concave

surface, by means of intensity-modulated radiation therapy (IMRT).

Possibly 30% of targets have concave surfaces. For example, the prostate, abutted by rectum and bladder, is kidney-bean shaped in transaxial cross section (Figure 3).

Many brain tumours, and tumours of the head and neck, similarly present a challenge to planning for invaginated surfaces. In other circumstances, when protecting the adjacent normal structures is more important than uniformly irradiating the target, IMRT presents an opportunity for this, so called, conformal avoidance. In short, the inclusion of modulation as a planning option widens the search space of opportunities to improve the dose distribution or, as physicists would say, “increases the number of degrees of freedom”. In even better summary, as Silvanus Thompson might have approved, “IMRT leads to better/tighter dose distributions”.

How IMRT?

Imaging and planning for IMRT

One might say that, even if the concepts had been understood and the technology had been available, IMRT before 1972 would have made no sense. Although X-ray CT was in late gestation before this date [18] the year 1972 saw the birth of commercial CT and by 1976 had been both developed and extensively commercialised. For the first time diagnostic radiologists knew more precisely the three-dimensional (3D) geometry of the tumour (or at least the 3D geometry as measured by changed X-ray attenuation). Radiotherapists were quick to see the potential of planning for better treatment. So (to quote Harold Johns) “if you can't see it you can't hit it and if you can't hit it you can't cure it”. Changing negative to positive and invoking “Silvanus-Thompson speak”: seeing the tumour we can aim at it and aiming radiation more accurately we can possibly cure it. 3D imaging is the most important component of modern radiation therapy and other 3D techniques such as MRI, SPECT and PET showing functional changes add to the ability to understand better the tumour extent and to plan the correct 3D target.

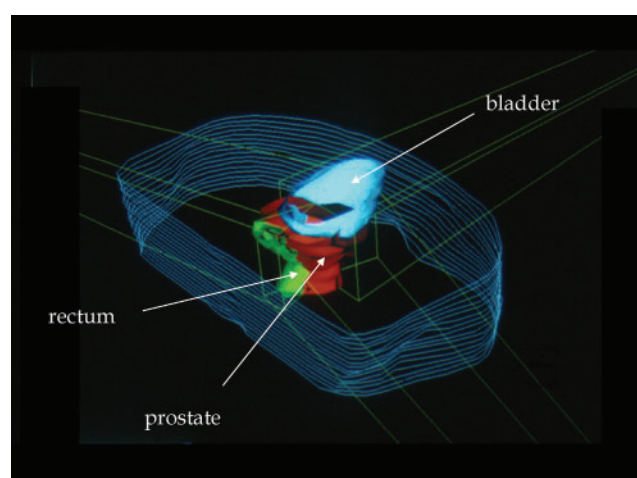


Figure 3. Shows a “classic” application for IMRT, to conform the high dose to the non-uniform shape of the prostate simultaneously sparing dose to normal rectum and bladder.

Once the 3D images are obtained (Figure 4) the human patient is essentially disposed of, for the planning stage. The patient “becomes an array of voxels”. Using these, contours of the target are drawn on selected slices. The contours can be merged to create 3D target shapes (and similarly for organs-at-risk [OAR]). Beam directions can be chosen to substantially avoid OAR and the weights of radiation from different beams can be computed such that when added together the required shape of the high-dose volume is obtained so far as the physics of the photon-tissue interaction will allow. If the beams are just geometrically shaped, but otherwise are of uniform radiation, this is called geometrically conformal radiation therapy (CFRT). If the sub-components of each beam, the beamlets or bixels, have different intensities then this is IMRT.

Traditionally for 3D CFRT treatment planning has been done by “forward techniques”. The dose distribution is prescribed; the planner tries a number of different combinations of beam direction and weight until they are “satisfied” that the result is “as good as possible”. This is informed guesswork but somehow quaintly out of synchrony with the input technology. “Inverse planning” conversely informs a computer of the prescription, the constraints on the problem, both dosimetric and mechanical, certain preset choices such as number of beams, beam energy and maybe directions and then a computer algorithm works out the modulations required (Figure 5).

This was unheard of 15 years ago and is now commonplace, well understood and almost automatic. Whilst there are still issues of debate and interest in inverse planning the problems are largely solved. A review written 4 years ago would have concluded that inverse planning is absolutely required for IMRT. Now many subtly modified forward-planning methods are being developed. One in particular directly optimizes a few geometrical shapes so they are easy to deliver and still generate sufficient modulation to not compromise conformality. Silvanus Thompson’s summary would have been: use 3D images wisely; prioritise the importance of the selection of the target. Decide which parameters will be fixed and which will be computer optimized. Use the algorithms available but check their predictions against the requirements

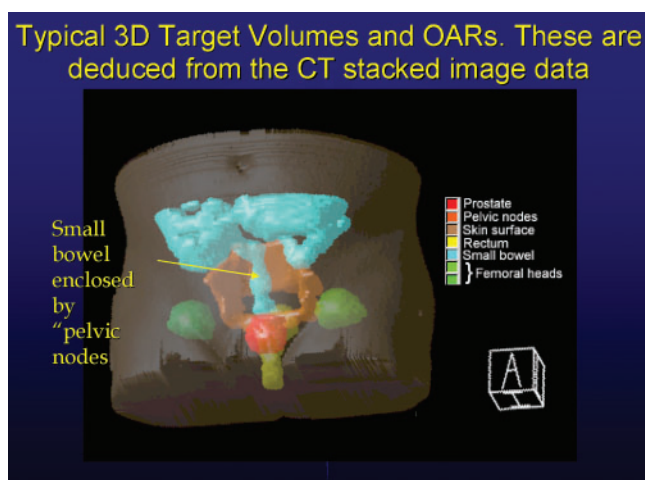


Figure 4. 3D data deduced from X-ray CT images. OAR, organ at risk.

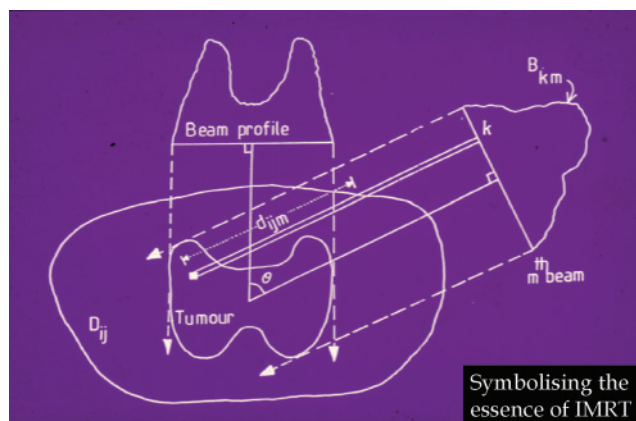


Figure 5. Just two (of several) modulated beams create an invaginated contour for the high-dose volume.

manually. Use the simplest modulation that does the job (which will vary from target to target).

Delivery of IMRT

There are two main classes of ways to modulate the beam intensity for IMRT: (i) those which do so by spatial variation directly and (ii) those which achieve the same spatial modulation by temporal means. In class (i) are the compensator, the multiple-static multileaf collimator (MSF MLC) method. In class (ii) are tomotherapy, the dynamic MLC (dMLC) technique, swept pencils, the scanning bar. Robotic IMRT is hard to classify having aspects of both (see later).

IMRT by spatial variation

If a piece of metal of varying thickness is put between source and patient fewer X-rays per unit time emerge where the metal is thickest and vice versa. Since X-ray attenuation is exponential, the relationship between thickness and intensity is non-linear. This method of modulating the intensity has been in use since the mid 20th century and the metal devices are called compensators (Figure 6).

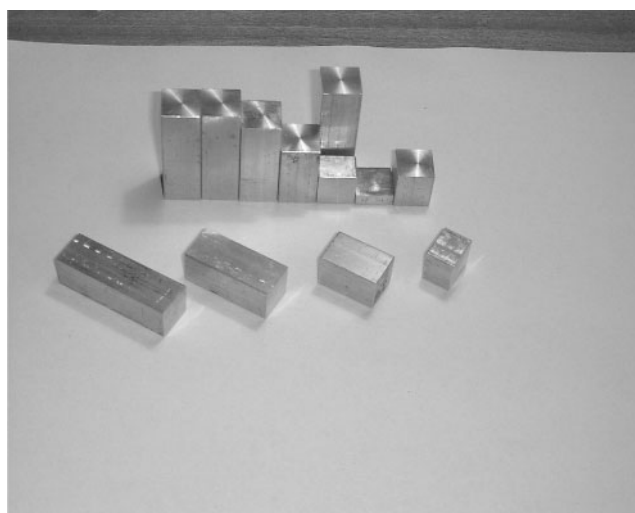


Figure 6. Components of an “Ellis compensator”.

They can be built of LegoTM-like blocks (Ellis compensator), of thin sheets of lead glued together, of cast metal, of poured lead or tungsten granules, of piston-deformed lead putty and a host of equivalents. Mostly they were designed for missing tissue compensation, hence their name. Early users would not have recognised the words IMRT in connection with their use. They still have their strong supporters given that their spatial resolution is not limited by any collimation, they can have a large dynamic range with continuous intensity levels and they suffer no artefacts from collimation leaves and require no verification of collimation. They also have a very “Silvanus Thompson simplicity” of understanding. “Less comes out where the metal is thickest”. Any fool can understand them. A more clever fool will recognise that there are some more complex issues such as the need to consider beam hardening, scatter, minimum-intensity level and so on.

The so called MSF-MLC technique (Figure 7) is predicated on the fact that if several fields of different geometrical shape and different intensities are superposed (from the same direction) then a modulated intensity will result. Given the widespread availability of the MLC and that it is supported by all of the major electrotechnical manufacturers for IMRT, this is now becoming a method of choice for implementing IMRT. The pioneering experiment showing this technique was made by Bortfeld and Boyer in 1993, by hand-resetting each subfield and delivering a modulation to a sliced-bread phantom (body phantom in slices with film sandwiched in the slices).

The films were digitised and 3D plots of dose were drawn by hand (Figure 8).

Clearly any fool can visualize how this works. Yet this is an area of IMRT with which Silvanus Thompson would have been particularly grumpy. The papers on techniques to decompose modulated fields into subcomponents have become impossibly complicated, maybe unnecessarily so. Mathematicians, group theorists and graph theorists have waded in and developed a bewildering armament of methods. As far as this fool can understand, the paper by Langer et al [19] presents the best and definitive method to

decompose modulated fields with minimum number of both components and monitor units (so giving the fastest treatment time and the smallest chance of leakage contamination). But this fool may not have the complete picture because there are still papers appearing claiming unsolved issues.

IMRT by temporal variation

A spatial modulation of intensity will be generated if a pair of jaws moves from a position of total closure one side of a field to total closure at the other side, varying the width between the jaws *en route*. To a first approximation the intensity at any point in the field will be given by the difference between the arrival time of the trailing jaw and that of the leading jaw. If the field is instead broken up into strips with each strip irradiated by a pair of MLC leaves then the same statement holds for each leaf track. The resulting field is then modulated in 2D. Any fool can see that. A more clever fool will observe that this is further complicated by leaf transmission (leakage), interleaf leakage, behaviour in the regions of the tongues and grooves of the leaf sides, head scatter from the collimation, finite spot size of radiation focal spot, effects of gravity on the MLC, effects of mispositioning of MLC leaves and errors due to the difficulty of precise positioning, machine constraints on interdigitation, effects of finite maximum leafspeed, effects of finite acceleration and deceleration times and so on. Many papers and reviews sort out these difficulties which are now largely understood. The resulting delivery technique is called the dynamic MLC (dMLC) method. It was the one first used by Elekta although all the accelerator manufacturers now offer MSF-MLC instead.

A totally different method of generating a spatial modulation through temporal modulation is tomotherapy which may be either slice-based or spiral. In slice-based tomotherapy the radiation is collimated to a narrow slit longitudinally.

In the slit beam resides a **multivane intensity modulating collimator (MIMiC)** with attenuating vanes which may

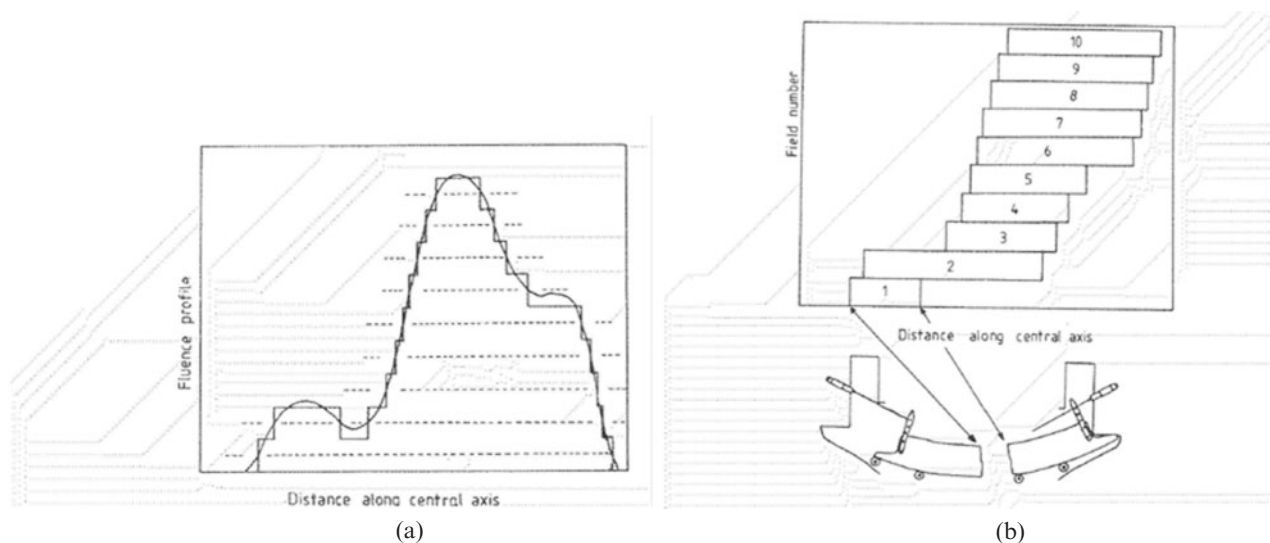


Figure 7. Essence of the multiple-static multileaf collimator (MSF-MLC) technique. Thomas Bortfeld first described the step-and-shoot MLC technique in 1993. (a) Approximate profile by steps. (b) Leaf sweep realisation.

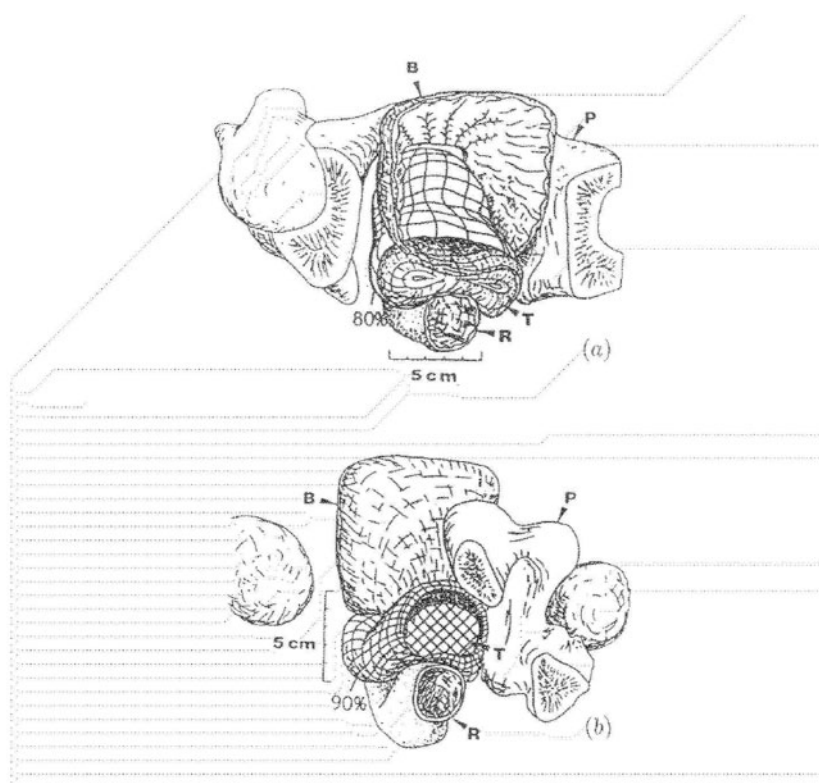


Figure 8. Pre-computer-3D dose display by Art(ist) Boyer. In 1993 Thomas Bortfeld and Art Boyer made the first IMRT step-and-shoot delivery in Houston using a Varian machine and taking about 3 hours to reset fields by hand. They drew this graphic 3D display of dose.

move into the slit for pre-defined times. Where the dwelltime of the vane is highest the intensity will be lowest and vice versa. As the vanes execute their motion the gantry rotates almost a full circle. A 2D conformal dose results in the irradiated slice (in practice two slices are irradiated together as there are two sets of vanes per slice – one from each side). To irradiate a larger volume the patient is shunted along by a slice width and the process repeated. Any fool can see that. A more clever fool will consider the effects of slice abutment, the effects of adjacent vane interference, the finite push-pull time of the vanes, intervane and through-vane leakage, tongue-and-groove effects, head scatter, the effect of larger numbers of MUs, stability of rotation speed, correction for glitched vane transitions and so on. This form of tomotherapy was first introduced by the NOMOS Corporation in 1992 and the first patients were treated in March 1994. The technology had the clinical competitive lead for several

years over any other form of IMRT (except of course compensators).

Now imagine that instead of two banks of vanes there is just one and that the gantry rotates continuously through many revolutions and that the patient slides longitudinally simultaneously and one has the alternative spiral Tomotherapy, the design pioneered in 1993 by Rock Mackie and commercially available since 2002 (Figure 9). Any fool can see the basic workings but a more clever fool is needed to grasp the concepts of pitch, pitch artefacts, modulation factors, transmission effects, leakage, etc.

The main methods of IMRT delivery have now been mentioned, and those in regular clinical use. Less used but conceptually possible are IMRT through sweeping a pencil beam in which the intensity is proportional to the dwelltime of the beam, sweeping a 1D attenuating bar, in which the intensity decreases with increasing dwelltime

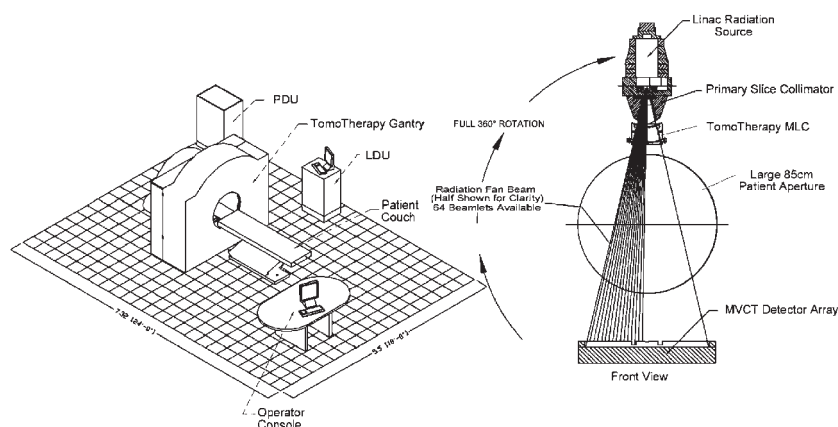


Figure 9. Tomotherapy.

and the use of the robotic Cyberknife to which we shall return.

Clinical IMRT

The first clinical IMRT with modern technology for delivery was in March 1994 at Baylor College of Medicine using the NOMOS MIMiC technique for head and neck cancer. During 1995 IMRT via use of the conventional MLC began at Memorial Sloan Kettering Cancer Centre (MSKCC) in New York for treatment of the prostate. Clinical Tomotherapy began in August 2002. Whilst some bladder fields were modulated at the Christie Hospital, Manchester prior to this date, the first clinical IMRT in the UK in which all fractions of all fields were modulated took place at the Royal Marsden NHS Foundation Trust on September 20th 2000.

Short of writing a textbook (of which there are some already) on IMRT it is as futile to try to review all clinical IMRT as it is to review all the physics developments in detail. By the time of writing (July 2004) there are now hundreds of centres participating in clinical IMRT. There are also thousands of papers reporting the potential advantages of IMRT through analysis of improved dose distributions consequent on its use. However the number of IMRT implementations which report actual clinical benefit rather than potential or hoped-for benefit is still finite and just about countable.

That there is so little hard evidence for the utility of IMRT is for three reasons: (i) first in the USA, where the majority of clinical IMRT has been so far performed, there is a culture of implementing new technology "because it is there" based on principles of enterprise, financial insurance reimbursement and state-to-state/centre-to-centre equality. Some argue that fully randomized phase-3 trials are unlikely to be undertaken in the USA although there are a few notable exceptions; (ii) much of the predicted benefit of IMRT is in the reduction of late radiation normal-tissue complications which by definition are too early to observe; (iii) whilst the strongest "level-1" evidence for clinical utility will come from randomized trials, these are hard to set up and some are arguing that, given the unequivocally improved dose distributions, it may even be unethical to randomize patients when one arm is predicted poorer outcome. Altogether this is a complex debate.

Against this background now follows a brief list of studies which have shown actual clinical benefit of IMRT:

- (i) Following dose escalation to the prostate at MSKCC fewer rectal complications have been observed than would have been observed with conventional radiotherapy [20].
- (ii) Mundt et al [21] reported absence of high-grade early gastrointestinal and genitourinary toxicity in IMRT of the pelvis for gynaecological malignancy.
- (iii) De Meerleer et al [22] and Teh et al [23] reported reduced rectal toxicity in groups of patients receiving IMRT of the prostate.
- (iv) Following parotid-sparing IMRT for oropharyngeal carcinoma at the Mallinckrodt Institute of Radiology salivary flow measurements showed

improved late parotid function compared with conventional radiotherapy [24].

- (v) Maes et al [25] have shown reduced xerostomia following bilateral elective neck irradiation. Kwong et al [26], Patel et al [27], Lee et al [28] and Münther et al [29] have also shown reduced xerostomia.
- (vi) Claus et al [30] have shown reduced dry-eye syndrome following IMRT for sinonasal tumours.
- (vii) Yarnold et al [31] have presented a preliminary analysis of a randomized phase-3 trial between IMRT of the whole breast and conventional 2-tangent irradiation. A change in breast appearance was scored in 52% of patients in the conventional arm but only 36% of patients in the IMRT arm.
- (viii) Finally there have been several trials showing improved clinical outcome of geometrically conformal CFRT but these, not being IMRT, are not listed here.

Examples of clinical IMRT from the Royal Marsden NHS Foundation Trust

It was shown in the mid-to-late 1990s that by modulating the intensity of the two tangential fields the dose homogeneity to the breast could be improved [32]. Subsequently a phase-3 randomized trial was completed with 160 women in each arm of the trial comparing conventional unmodulated tangential-field irradiation with modulated tangential fields. The results are being analysed [31].

The first pelvic clinical IMRT at the Royal Marsden NHS Foundation Trust was a phase-1 trial of IMRT of prostate plus pelvic nodes. The goal was to deliver 70 Gy to the prostate and initially 50 Gy to pelvic lymph nodes, subsequently escalated to 55 Gy and 60 Gy. The small-bowel toxicity was minimized by keeping dose less than 45 Gy. Five fields were selected (PA, L- and R-lateral and AO at $\pm 30^\circ$ to anterior). The treatments were carried out at both Sutton and Chelsea branches of the hospital. At Sutton, planning was initially using the NOMOS CORVUS system, then the Nucletron HELAX system and then the ADAC PINNACLE system [33]. Treatment planning at Chelsea used the Varian HELIOS system. Treatment at Sutton was on Elekta accelerators and at Chelsea on Varian accelerators [34]. Initially at Sutton the Elekta dMLC technique was used, subsequently changed to step-and-shoot. Quality was assured by repeating a Bortfeld-Boyer experiment (Figure 10) on an anthropomorphic phantom with film and thermoluminescent dosimeters (TLDs) and also by irradiating film strapped to the gantry head. The work at Sutton was performed in the context of the Elekta International IMRT Consortium. The first patient was treated at Sutton in September 2000 and at Chelsea in July 2001.

Head and neck IMRT commenced at Chelsea in April 2002 and at Sutton in August 2003. Class solutions were developed for the larynx, base of tongue and thyroid tumours with involved neck nodes. The target dose was 65 Gy and nodal dose 54 Gy with the challenge to protect the spinal cord and oesophagus and parotid glands.

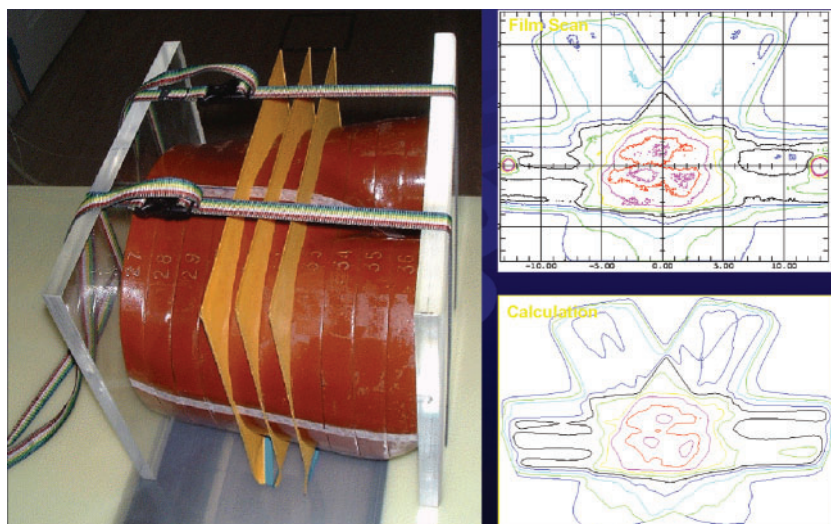


Figure 10. Quality assurance of the pelvic IMRT via a Bortfeld-Boyer experiment. Upper right shows the measured dose distribution in a slice and lower right shows the calculated distribution.

The future of technology for IMRT

Solutions already exist for planning and delivering IMRT and clinical work is well underway. This is not to say that there are no unsolved problems in planning and delivery but there may be areas better worthy of the limited research resources available. We are very good at depositing highly conformal dose distributions to targets that are unequivocally determined in tissue-equivalent material and in absolutely static patients. However, patients move and targets are not unequivocally determined by X-ray CT. Hence the growth area is image-guided (IG) radiation therapy (IG-IMRT). Images, both anatomical and functional, may be used to improve target definition to account for differences in hypoxia and tumour proliferation. Imaging can also be used to monitor the motion of internal organs and to plan image-guided treatment delivery.

As an example of the use of imaging to plan therapy Cu(II) diacetyl-bis methylthiosemicarbazone (ATSM) has been used to image tumour hypoxia [35] and it can be speculated that, knowing the distribution of hypoxia, “dose painting” can be performed delivering deliberately inhomogeneous dose to the tumour [36]. A second example is that if SPECT uptake of radiopharmaceutical shows areas of unperfused lung then these could be useful pathways into lung tumours compared with passing radiation through well perfused lung.

External intrafraction tissue motion can be observed by imaging active or passive infrared markers or optical interferometry. Internal intrafraction tissue motion can be observed by X-ray imaging of implanted (gold grain) markers [37], by ultrasound [38] and by magnetic monitoring [39]. Outstanding research issues include: (i) how to relate internal to external motion [40] (Figure 11); (ii) how to intervene therapy via gating [41], breath-hold [42], forced breathing [43], active breathing control [44] or tracking [40]; (iii) whether to believe the reproducibility of intrafraction motion.

What might Silvanus Thompson have made of IMRT in 2004?

Albeit that the invoking of the name of Silvanus Thompson throughout this text is clearly an artificial

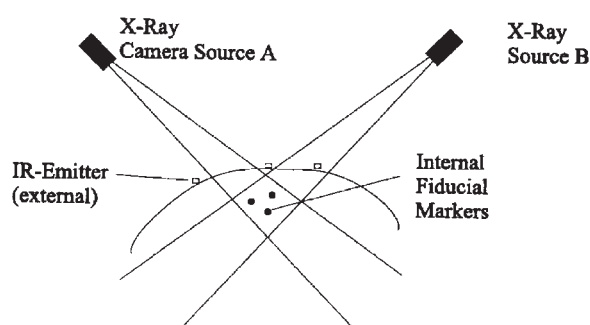


Figure 11. The motion of internal markers is detected by X-rays; motion of external markers is detected by infrared. Motions are correlated every 10 s. Monitor of external markers by infrared then translates to movement of internal tumour markers in almost real-time and this is fed back to the robot [40].

construct, it nevertheless reminds us to “strip away the unwanted complexity” as he would have done when teaching. So what would he have made of the IMRT scene in 2004 and what would he have extracted for teaching? Clearly whatever I write is surmise but it serves as a conclusion as it did in my Lecture. Silvanus would have said:

- (i) In 1988 when inverse planning seriously began there was no IMRT delivery equipment except the compensator;
- (ii) In 1992 MIMiC slice tomotherapy became available;
- (iii) In 1994 the MLC MSF and the dMLC method had been operated by a few centres in a research setting;
- (iv) By the mid 1990s all the main planning techniques had been worked out and the main methods of IMRT delivery had been shown to work at least in a research setting;
- (v) By 2000 commercial MLC/Linac manufacturers had made available MSF-MLC and dMLC technique linked to inverse planning;
- (vi) In 2004 the MIMiC has still delivered the most IMRT but the MLC techniques are catching up;
- (vii) Many centres in Europe, USA and Asia regard IMRT as a clinical necessity;
- (viii) Clinical implementation still requires multiskills of doctors, physicists, radiographers, engineers all working together. It is not quite “turn key”;



Figure 12. The press has been interested following David Dearnaley's initiative.

- (ix) Patients will use the internet to seek "best treatment"; be prepared for that;
- (x) The press will publicise IMRT (Figure 12). This is good for showing the positive side of radiation and for encouraging interest and investment in medical technology. It may not be so good for patients and relatives who expect the advertised wares to be widely and immediately available;
- (xi) Watch out for robotics (especially for motion correction), for simpler IMRT (to meet a call from less well off places) and (possibly and sadly) an anti-IMRT backlash from diehards.

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